

## Research Article

# The Importance of Lipid Raft Proteins for Sepsis: Could Raftlin-2 be a New Biomarker?

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### Abstract

**Objectives:** Bacterial infections and sepsis are common problems in patients receiving intensive care unit treatment. Raftlin-2 is a protein with an important role in lipid rafts, and the aim of this study was to compare raftlin-2 micro protein blood levels in a healthy control group with a patient group with septicemia.

**Methods:** A prospective, controlled study was conducted in the intensive care unit (ICU) of a university hospital and a control group was selected from healthy individuals. There were 64 ICU patients and 74 individuals in the control group. Blood samples were taken from the study group before the start of antibiotic therapy. The C-reactive protein, procalcitonin, lactate, biochemistry, and raftlin-2 levels of the patient and control groups were compared.

**Results:** There was a statistically significant difference between the lactate levels in the healthy group and the patient group with septicemia, but not in the raftlin-2 protein level. The p-values were calculated at 0.350 for raftlin-2 and 0.007 for lactate. There was a statistically significant difference between the 2 groups in the level of procalcitonin ( $p=0.000$ ), high-density lipoprotein (HDL) ( $p=0.0001$ ), low-density lipoprotein (LDL) ( $p=0.0001$ ), white blood cells ( $p=0.001$ ), and ferritin level ( $p=0.0001$ ).

**Conclusion:** In this study, the LDL and HDL levels of patients with sepsis were lower than those of the control group. Low LDL and HDL levels may be associated with sepsis. However, there is a need for prospective, controlled, and extensive participatory studies to further examine the lipid profile of patients. In this study, the raftlin-2 level was not significantly different between the patient and the control group. These findings suggest that measurement of raftlin-2 level does not constitute an alternative to the diagnostic methods used in clinics for sepsis. Additional studies are needed to determine the benefits of measuring the raftlin-2 level in clinical use and in the experimental setting.

**Keywords:** High-density lipoprotein, low-density lipoprotein, procalcitonin, Raftlin-2, sepsis

Bacterial infections and sepsis are common problems in patients receiving intensive care unit treatment. Sepsis and septic shock are among the major causes of death

worldwide. 56-91 deaths per 100.000 deaths were caused by sepsis or septic shock. In patients with sepsis and severe sepsis, the mortality rate was 30% to 50%, while in

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septic shock patients, the rate was reported as 80%.<sup>[11]</sup> In septic shock patients, the delay of appropriate antibiotic treatment increased the mortality rate by 7.6% per hour.<sup>[2]</sup> For this reason, early diagnosis and treatment of sepsis has an important role in reducing mortality.<sup>[3]</sup> Endotoxins and proinflammatory cytokines released during the course of sepsis cause cascade activation in the endothelial cells, deterioration of the endothelial barrier and interruption of homeostasis.<sup>[4]</sup> In the studies performed, cholesterol and sphingolipid-rich microcellular regions recommended as lipid rafts which separated from plasma membrane and caveolae constituting the cytoskeleton and responsible for signal transduction were identified.<sup>[5-10]</sup>

Transmembrane proteins such as TCR (T cell receptor) and BCR (B cell receptor) interact with lipid rafts through cellular stimulation.<sup>[11, 12]</sup> Lipid rafts have been thought to try to provide better signal transmission by clustering with cellular stimulation.<sup>[13]</sup> Although raftlin-2 mRNA has been interpreted by the spleen and thymus and has been found in many immunocytes such as B and T cells, dendritic cells, and macrophages, raftlin -2 mRNA has been shown to be present only in splenic B cells.<sup>[14]</sup> Endothelial cascade activation and endothelial dysfunction are important in sepsis.<sup>[15]</sup> This determinant role of endothelium makes it even more meaningful to use biomarkers in the endothelial cascade.<sup>[16]</sup> Because of the important role of lipid raft in vascular inflammatory response,<sup>[17-19]</sup> we aimed to compare the level of raftlin2 micro protein, a raftlin-2 homologue, between patients with septicemia and healthy individuals.

## Methods

This prospective, controlled study was conducted in patients hospitalized in university hospital, 13-bed Internal Medicine Intensive Care Unit. On May 9, 2014, at the meeting no. 31, the study approval from the Ethics Committee of the Faculty of Medicine of Çukurova University was taken. 138 patients were included in the study between 01/05/2014-01/05/2015. 64 patients with sepsis were included in the study. This study is based on the criteria of sepsis defined in 2001 with the participation of American College of Chest Physicians (ACCP), Society of Critical Care Medicine (SCCM), American Thoracic Society (ATS), European Society of Intensive Care Medicine (ESICM) and Surgical Infection Society (SIS) associations.<sup>[20]</sup> Those younger than 18 years or those who were pregnant were removed from the study. The control group consisted of healthy volunteers. Blood samples were taken in the study group before the start of antibiotic therapy, without time loss for treatment. Blood from patients was studied in hospital central laboratory on the same day. Blood biochemical measurements were made using the same brand commercial measurement kits as the Dxl 800 model biochemical auto

analyzer device from Beckman Coulter (USA) and C - reactive protein (CRP) measurement using the same brand commercial measurement kit as the Immage-800 model of the same company. Procalcitonin (PCT) and Brain Natriuretic Peptide (BNP) measurements were made using the same brand commercial measurement kits as the Cobas E411 biochemistry autoanalyzer device from Roche Diagnostic (Switzerland). Complete blood count was performed using the same brand commercial measurement kits as the XN-1000 device from Sysmex (USA). Venous blood samples were centrifuged at 5.000 rpm for 10 minutes for raftlin-2 study, then the resulting plasma was stored at -80°C. Raftlin-2 samples were collectively studied using the micro-ELISA (Enzyme-Linked Immunosorbent Assay) method using a research kit of Sunred Biological Technology (China).

Statistical analyzes were performed with SPSS 20.0 (Chicago IL, USA). For the intermittent and continuous variables, descriptive statistics were given as mean, standard deviation, median, minimum, maximum, number and percentage slice. Comparisons between groups were made by Student t-test when the parametric test assumptions were met; Mann Whitney-U test was used when the assumptions were not met. Chi-square test or Fisher's test was used to compare categorical data. ROC analysis was used to determine the cut-off values of LDL and HDL values for sepsis diagnosis. Statistical significance was accepted as  $p < 0.05$ .

## Results

The mean age of 138 individuals included in the study is  $58 \pm 16$  years. 75 were male (54.3%) and 63 were female (45.7%). There was no statistically significant difference in age and gender between sepsis and control groups (Table 1). PCT, CRP, WBC, Ferritin, lactate values were significantly higher in the patient group than the control group (Table 1). For BNP and raftlin-2, no statistically significant difference was found between the two groups.

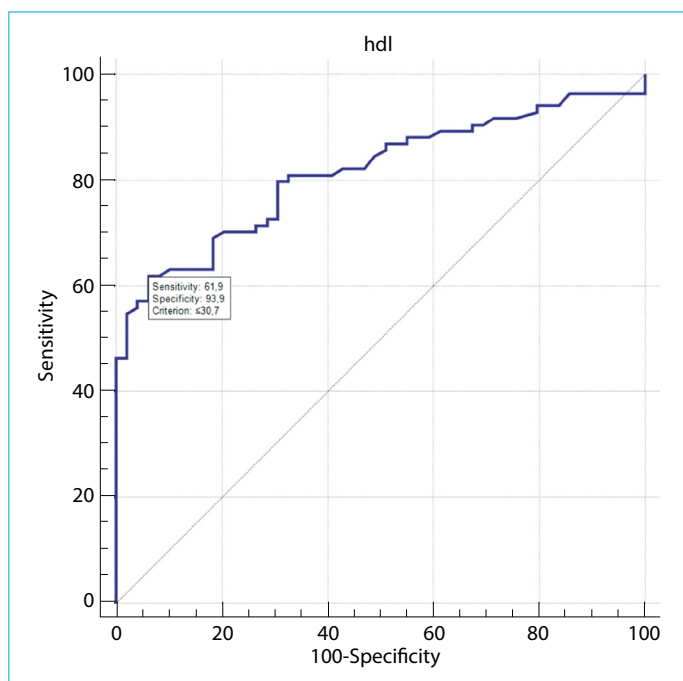
LDL in the sepsis group was  $63.6 \pm 48.4$  mg/dl whereas in the control group it was  $107.1 \pm 45.7$  mg/dl, HDL in the sepsis group was  $26.9 \pm 10.3$  mg/dl and in the control group it was  $50.3 \pm 99.0$  mg/dl and these were found statistically significantly lower.

In the ROC curve analysis performed for HDL the sensitivity was 61.9, specificity was 93.9, AUC was 0.815, confidence interval was between 0.739 and 0.877 and cut off value was 30.7 mg/dl Figure 1.

In the ROC curve analysis performed for LDL, the sensitivity was 86.7, specificity was 71.2, cut off value was 91 mg/dl, AUC was 0.783 and confidence interval was between 0.703 and 0.850 Figure 2.

**Table 1.** Demographic, clinical and laboratory findings of the study groups

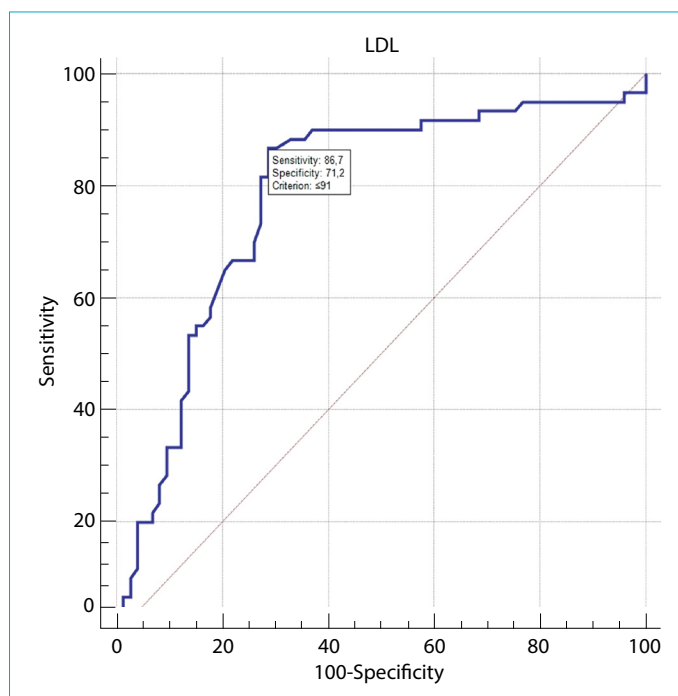
	Sepsis group	Control group	p
Age	58.7±19.5	59.0±13.3	0.917
Gender			
Male	39 (52.0)	36 (48.0)	0.148
Female	25 (39.7)	38 (60.3)	
LDL	63.6±48.4	107.1±45.7	0.0001
HDL	26.9±10.3	39.4±14.8	0.0001
PCT	32.13±34.62	0.21±0.30	0.000
CRP	20.22±12.92	2.62±5.58	0.0001
WBC	42174.8±78658.20	9571.27±6060.12	0.0001
LAKTAT	2.9544±2.20	1.6909±0.69619	0.007
BNP	15372.1000±13645.29	12361.8±13473.31	0.134
FERRITIN	2580.2820±3964.78	571.4±905.44	0.0001
RAFTLIN-2	24.8499±12.31	23.28±11.01127	0.350

**Figure 1.** ROC curve analysis performed for HDL.

## Discussion

In healthy individuals, procalcitonin is the precursor of the hormone calcitonin.<sup>[21]</sup> All cells and tissues have significant levels of procalcitonin mRNA. Procalcitonin produced in non-endocrine tissues cannot progress to calcitonin, and procalcitonin levels increase 3-6 hours after infection.<sup>[22]</sup> In many studies PCT increase was associated with severe sepsis and septic shock development <sup>[23-26]</sup>, in our study, procalcitonin values were similarly high in patients with septicemia.

CRP is a pentameric protein that produced by liver, an acute phase reactant and stored in inflamed tissue which is

**Figure 2.** ROC curve analysis performed for LDL.

discovered by Tillet and Francis in 1930, reacts with the somatic 'C' carbohydrate antigen of the capsule of pneumococcus.<sup>[27, 28]</sup>

CRP and PCT were found to be good markers for sepsis and survey in septicemic patients in ICU.<sup>[2, 29-33]</sup> Many studies have shown that white blood cell counts, CRP and ferritin levels are high in infected patients<sup>[34, 35]</sup>, in this study, CRP, ferritin, white blood cell values were significantly higher in the septicemia group.

Various lipid disorders are seen in intensive care patients such as <sup>[36]</sup>, elevated triglycerides; reduced low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels.<sup>[37, 38]</sup>

Treating hyperlipidemia with HDL medications for the prevention and treatment of endotoxemia has been proposed as a new treatment approach.<sup>[36, 39]</sup> The results in this study also supported these studies and in the ROC curve analysis performed for HDL the sensitivity was 61.9, specificity was 93, 9 and cut off value was 30.7 mg/dl. In the ROC curve analysis performed for LDL, the sensitivity was 86.7, specificity was 71.2, cut off value was 91 mg/dl, AUC was 0.783 and confidence interval was between 0.703 and 0.850.

Lactate is produced by most cells. The ratio between hemodynamics and lactate level depends on the balance between the production and consumption of lactate. The lack of oxygenisation of the cell and the increased production of pyruvate by increased glycolysis leads to an increase in lactate production.<sup>[40]</sup> In the early phase of septic shock, it has been shown that lactate levels increase even before liver blood flow and mitochondrial oxygen delivery have deteriorated.<sup>[41]</sup> We also found no statistically significant difference in lactate levels between the two groups in this study, which suggests that exclusion of patients with septic shock may have caused this.

The plasma level of raftlin-2 protein was  $24.8499 \pm 12.31$  in the patient group with septicemia,  $23.28 \pm 11.01127$  in the control group and p value between these two groups were 0.350, which was statistically insignificant. In contrast to the study by Lee et al., who compared the raftlin-2 protein levels of healthy subjects and patients with sepsis, severe sepsis and septic shock in intensive care unit, we did not find any statistically significant difference comparing septicemic group to the healthy subjects in terms of raftlin-2 protein levels.<sup>[42]</sup> In another study where raftlin-2 was studied for T cell mediated signal pathways and autoimmune side effects via Th17 shown that although Raftlin mRNA has been interpreted by the spleen and thymus and has been found in many immunocytes such as B and T cells, dendritic cells, and macrophages, raftlin-2 mRNA has been shown to be present only in splenic B cells.<sup>[14]</sup> It is possible that the results of our study and the results of Lee and his colleagues study differed because the cases with autoimmune disease were not excluded from the study. In the future clinical trials for raftlin-2, we recommend that those with autoimmune disease be excluded from the study, in order to increase the accuracy of the results.

## Conclusion

In our study, the LDL and HDL levels of patients with sepsis were lower than the control group. Low LDL and HDL levels may be associated with sepsis. However, there is a need for prospective, controlled and extensive participatory studies to determine the lipid profile of patients, the change in lip-

id values after admission, and the diagnosis and prognosis of sepsis. In our study, raftlin-2 levels were not significantly different between patient and control groups. Measurement of raftlin-2 levels does not constitute an alternative to the diagnostic methods used in clinics for sepsis. Additional studies are needed to determine the benefits of measuring the raftlin-2 levels in clinical use and in the experimental setting. We recommend exclusion of cases with autoimmune diseases when clinical trials are repeated.

## Disclosures

**Ethics Committee Approval:** This prospective, controlled study was conducted in patients hospitalized in university hospital, 13-bed Internal Medicine Intensive Care Unit. On May 9, 2014, at the meeting no. 31, the study approval from the Ethics Committee of the Faculty of Medicine of Çukurova University was taken.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** This study was supported by the Scientific Research Project Fund of the Faculty of Medicine of Çukurova University, BAP No: 2610 (06/05/2014). There is no conflict of interest with any institution, organization or person in this study.

**Authorship contributions:** Concept – H.E.S., M.E.; Design – H.E.S., M.E.; Supervision – H.E.S., E.K.; Materials – H.E.S., T.K., M.Y., M.E.; Data collection &/or processing – H.E.S., M.E., M.Y., T.K., S.C., F.K.; Analysis and/or interpretation – H.E.S., F.K., S.C., O.O.K.; Literature search – H.E.S., E.K., M.E., O.O.K.; Writing – H.E.S., E.K., M.E., O.O.K.; Critical review – H.E.S., E.K., O.O.K.

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